EXHIBIT AC

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Dated: December 17, 2007 Signature: _____
(Rosemarie Puljic-Salmeron)

Docket No.: 543312000401
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ravinder S. DHALLAN

Confirmation No.: 8885

Application No.: 11/212,812

Art Unit: 1634

Filed: August 26, 2005

Examiner: E. Whisenant

For: METHODS FOR DETECTION OF GENETIC DISORDERS

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

This is in response to the non-final Office Action dated June 15, 2007 (Part of Paper No./Mail Date 20070606), for which a response was due on September 15, 2007. Filed herewith is a Petition and fee for a three-month extension of time, thereby extending the deadline for response to December 15, 2007. Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

Amendments to the Claims are reflected in the listing of claims, which begins on page **2** of this paper.

Remarks/Arguments begin on page **10** of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (currently amended) A method for detecting a free nucleic acid, wherein said method comprises: (a) isolating free nucleic acid from a ~~nucleic acid containing~~ sample, wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor ~~was added to the sample~~; and (b) detecting the presence or absence of the free nucleic acid.

2. (Original) The method of claim 1, wherein said sample is obtained from a source selected from the group consisting of bacteria, viruses, fungi, mycobacteria, protozoa, molds, yeasts, plants, humans, non-humans, multi-cellular parasite, animals, and archeabacteria.

3. (Original) The method of claim 2, wherein the sample is obtained from a human source.

4. (Original) The method of claim 1, wherein the sample is obtained from a source selected from the group consisting of: a cell, fetal cell, tissue, blood, serum, plasma, saliva, urine, tear, vaginal secretion, umbilical cord blood, chorionic villi, amniotic fluid, embryonic tissue, lymph fluid, cerebrospinal fluid, mucosa secretion, peritoneal fluid, ascitic fluid, fecal matter, or body exudates.

5. (Original) The method of claim 4, wherein said sample is blood.

6. (Original) The method of claim 5, wherein said sample is obtained from plasma from said blood.

7. (Original) The method of claim 1, wherein said nucleic acid contains at least one mutation.

8. (Original) The method of claim 7, wherein said mutation is selected from the group consisting of: single point mutation, multiple point mutations, an insertion, a frameshift, a truncation, a deletion, a duplication, and a transversion.

9. (currently amended) The method of claim 7, wherein said mutation is in a gene selected from the group consisting of: BRCA1, BRCA2, MSH6, MSH2, MLHl, RET, PTEN, ATM, H-RAS, p53, ELAC2, CDHl, APC, AR, PMS2, MLH3, CYP1A1, GSTP1, GSTM1, AXIN2, CYP19, MET, NAT1, CDKN2A, NQ01, trc8, RAD51, PMS1, TGFBR2, VHL, MC4R, POMC, NROB2, UCP2, PCSK1, PPARG, ADRB2, UCP3, glur1, cart, SORBS1, LEP, LEPR, SIMl, TNF, IL-6, IL- 1, IL-2, IL-3, ILlA, TAP2, THPO, THRB, NBS1, RBM15, LIF, MPL, RUNX1, Her-2, glucocorticoid receptor, estrogen receptor, thyroid receptor, p21, p27, K-RAS, N-RAS, retinoblastoma protein, Wiskott-Aldrich (WAS) gene, Factor V Leiden, Factor II (prothrombin), methylene tetrahydrofolate reductase, cystic fibrosis, LDL receptor, HDL receptor, superoxide dismutase gene, SHOX gene, genes involved in nitric oxide regulation, genes involved in cell cycle regulation, tumor suppressor genes, oncogenes, genes associated with neurodegeneration, and genes associated with obesity.

10. (currently amended) The method of claim 1, wherein said free nucleic acid is from a species different from the species from which the sample was taken.

11. (Original) The method of claim 10, wherein said different species is from a group consisting of bacteria, viruses, fungi, mycobacteria, protozoa, molds, yeasts, plants, humans, non-humans, multi-cellular parasite, animals, and archeabacteria.

12. (Original) The method of claim 11, wherein said different species is a bacteria.

13. (Original) The method of claim 12, wherein said bacterial species is a gram-positive or gram-negative bacteria.

14. (currently amended) The method of claim 13, wherein said bacteria is selected from the group consisting of: Acidaminococcus, Acinetobacter, Acinetobacter Iwoffi, Aeromonas, Alcaligenes, Bacteroides, Bordetella, Branhamella, Brucella, Calymmatobacterium, Campylobacter, Cardiobacterium, Chromobacterium, Citrobacter, Citrobacter freundii, Coliform group, Edwardsiella, Enterobacter, Enterobacter sakazaki, Enterobacter aerogenes, Enterobacter cloacae, Enterobacter agglomerans, Enterococcus, Enterococcus faecalis, Enterococcus faecium, Escherichia, Escherichia coli, Escherichia coli-O157, Flavobacterium, Francisella, Fusobacterium, Haemophilus, Hafnia alvei, Klebsiella, Klebsiella oxytoca, Klebsiella pneumoniae, Legionella, Moraxella, Morganella, Morganella morganii, Neisseria, Pasturella, Plesiomonas, Proteus, Providencia, Proteus mirabilis, Pseudomonas, Pseudomonas aeruginosa, Salmonella, Salmonella typhimurium, Serratia, Serratia marcescens, Shigella, Shigella flexneri, Streptobacillus, Veillonella, Vibrio, Vibrio cholera, Yersinia, ~~Yersinnia~~ Yersinia entercolitica, Xanthomanas maltophiia, Staphylococcus, Staphylococcus albus, Staphylococcus aureus, Streptococcus, Streptococcus dysgalacticae, Micrococcus, Peptococcus, Peptostreptococcus, Bacillus, Bacillus cereus, Clostridium, Lactobacillus, Listeria, Listeria monocytogenes, Erysipelothrix, Propionibacterium, Eubacterium, and Corynebacterium.

15. (Original) The method of claim 11, wherein said different species is a virus.

16. (Original) The method of claim 15, wherein said virus is a DNA virus or an RNA virus.

17. (Original) The method of claim 15, wherein said virus is selected from the group consisting of: retrovirus, pathogenic virus, non-pathogenic virus, drug-resistant virus, drug-sensitive virus, adeno-associated virus, bird flu virus, cauliflower mosaic virus, cytomegalovirus (CMV), dengue virus, Epstein-Barr virus, feline leukemia virus, flavivirus, haemophilus influenza, hemorrhagic fever viruses, hepatitis virus including hepatitis A, B, C, and E, viruses, herpes simplex virus, human herpesvirus type A and B, human immunodeficiency virus (HIV), human papilloma virus, human T-cell lymphotrophic virus, HTLV Type I, HTLV Type II, influenza virus, Japanese encephalitis virus, moraxella catarrhalis, non-typeable haemophilus, reovirus, parainfluenza, parvovirus, papova virus, Respiratory syncytial virus, Rubella virus, rotavirus, SARS, tomato bushy stunt virus, varicella-zoster virus, and vaccinia virus.

18. (Original) The method of claim 11, wherein said different species is a fungus.

19. (Original) The method of claim 18, wherein said fungus is a drug-sensitive fungus or a drug-resistant fungus.

20. (Original) The method of claim 18, wherein said fungus is selected from the group consisting of: Candida, Candida albicans, Candida tropicalis, Candida parapsilosis, Candida stellatoidea, Candida krusei, Candida parakrusei, Candida lusitanae, Candida pseudotropicalis, Candida guilliermondi, Candida glabrata, Aspergillus, Aspergillus fumigatis, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus, Aspergillus sydowi, Aspergillus flavatus, Aspergillus glaucus, Cryptococcus, Histoplasma, Coccidioides, Paracoccidioides, Blastomyces, Basidiobolus, Conidiobolus, Rhizopus, Rhizomucor, Mucor, Absidia, Mortierella, Cunninghamella, Saksenaea, Pseudallescheria, Sporotrichosis, Fusarium, Trichophyton, Trichosporon, Microsporum, Epidermophyton, Scytalidium, Malassezia, Actinomycetes, Sporothrix, Penicillium, Saccharomyces and Pneumocystis.

21. (currently amended) The method of claim 1, wherein isolation of free nucleic acid comprises a centrifugation step.

22. (Original) The method of claim 21, wherein the centrifugation step is performed with the centrifuge braking power set to zero.

23. (Original) The method of claim 21, wherein the centrifugation step is performed at a speed selected from the group consisting of 0-50 rpm, 50-100 rpm, 100-200 rpm, 200-300 rpm, 300-400 rpm, 400-500 rpm, 500-600 rpm, 600-700 rpm, 700-800 rpm, 800-900 rpm, 900-1000 rpm, 1000-2000 rpm, 2000-3000 rpm, 3000-4000 rpm, 4000-5000 rpm, 5000-6000 rpm, 6000-7000 rpm, 7000-8000 rpm, and greater than 8000 rpm.

24. (Withdrawn) A composition comprising mutant DNA and normal DNA, wherein the percentage of free mutant DNA in the total free DNA of the composition is selected from the group consisting of: about 5-10% free mutant DNA, about 10-13% free mutant DNA, about 13-15% free mutant DNA, about 15-16% free mutant DNA, about 16-17% free mutant DNA, about 17-18% free mutant DNA, about 18-19% free mutant DNA, about 19-20% free mutant DNA, about 20-21% free mutant DNA, about 21-22% free mutant DNA, about 22-23% free mutant DNA, about 23-24% free mutant DNA, about 24-25% free mutant DNA, about 25-35% free mutant DNA, about 35-45% free mutant DNA, about 45-55% free mutant DNA, about 55-65% free mutant DNA, about 65-75% free mutant DNA, about 75-85% free mutant DNA, about 85-90% free mutant DNA, about 90-91% free mutant DNA, about 91-92% free mutant DNA, about 92-93% free mutant DNA, about 93-94% free mutant DNA, about 94-95% free mutant DNA, about 95-96% free mutant DNA, about 96-97% free mutant DNA, about 97-98% free mutant DNA, about 98-99% free mutant DNA, and about 99-99.7% free mutant DNA.

25. (Withdrawn) A diagnostic method comprising analyzing a composition comprising mutant DNA and normal DNA, wherein the percentage of free mutant DNA in the total free DNA of the composition is selected from the group consisting of: about 5-10% free mutant DNA, about 10-13% free mutant DNA, about 13-15% free mutant DNA, about 15-16% free mutant DNA, about 16-17% free mutant DNA, about 17-18% free mutant DNA, about 18-19% free mutant DNA, about 19-20% free mutant DNA, about 20-21% free mutant DNA, about 21-22% free mutant DNA, about 22-23% free mutant DNA, about 23-24% free mutant DNA, about 24-25% free mutant DNA, about 25-35% free mutant DNA, about 35-45% free mutant DNA, about 45-55% free mutant DNA, about 55-65% free mutant DNA, about 65-75% free mutant DNA, about 75-85% free mutant DNA, about 85-90% free mutant DNA, about 90-91% free mutant DNA, about 91-92% free mutant DNA, about 92-93% free mutant DNA, about 93-94% free mutant DNA, about 94-95% free mutant DNA, about 95-96% free mutant DNA, about 96-97% free mutant DNA, about 97-98% free mutant DNA, about 98-99% free mutant DNA, and about 99-99.7% free mutant DNA

26. (Original) The method of claim 1, wherein said method is used to detect, diagnose, or monitor a disease.

27. (Original) The method of claim 26, wherein said disease is cancer.

28. (Original) The method of claim 27, wherein said cancer is selected from the group consisting of: carcinoma of the bladder, breast, bronchial, colon, kidney, liver, lung, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin; small cell lung cancer, squamous cell carcinoma, hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkett's lymphoma, hematopoietic tumors of myeloid lineage, acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia, tumors of mesenchymal origin, fibrosarcoma and rhabdomyosarcoma, tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma and schwannomas, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

29. (Original) The method of claim 1, wherein said method is used to monitor response to treatment.

30. (Original) The method of claim 29, wherein the treatment is selected from the group consisting of surgery, radiation, lifestyle change, dietary protocol, supplementation and administration of a drug.

31. (Original) The method of claim 30, wherein the treatment is administration of a drug.

32. (currently amended) The method of claim 31, wherein said drug is selected from the group consisting of: chemotherapeutic agents, anti-bacterial agents, anti-viral agents, anti-fungal agents, targeted-cancer drugs, cytoxoic agents, cytostatic agents, anti-proliferative agents, Avastin, altretamine, busulfan, chlorambucil, cyclophosphamide, Erbitux, Rituxan, ifosfamide, mechlorethamine, melphalan, thiotepa, cladribine, fluorouracil, floxuridine, gemcitabine, thioguanine, pentostatin, methotrexate, 6-mercaptopurine, cytarabine, carmustine, lomustine, streptozotocin, carboplatin, cisplatin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, JM216, JM335, fludarabine, aminoglutethimide, flutamide, goserelin, leuprolide, megestrol acetate, cyproterone acetate, tamoxifen, anastrozole, bicalutamide, dexamethasone, diethylstilbestrol, prednisone, bleomycin, dactinomycin, daunorubicin, doxirubicin, idarubicin, mitoxantrone, losoxantrone, mitomycin-c, plicamycin, paclitaxel, docetaxel, CPT-11, epothilones , topotecan, irinotecan, 9-amino camptothecan, 9-nitro camptothecan, GS-211, etoposide, teniposide, vinblastine, vincristine, vinorelbine, procarbazine, asparaginase, pegaspargase, methoxtrexate, octreotide, estramustine, and hydroxyurea.

33. (cancelled)

REMARKS

Claims 1-33 are pending in the present application. Claims 24 and 25 have previously been withdrawn. By virtue of this response, claims 1, 9, 10, 14, 21, and 32 are amended, and claim 33 is cancelled. Accordingly, claims 1-23 and 26-32 are currently under consideration. Allowance of the pending claims is respectfully requested.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and, moreover, has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Amendments

The amendments to claims 1, 9, 10, 14, 21, and 32 are fully supported in the original application.

Claim 1 has been amended to indicate that the nucleic acid recited therein is free nucleic acid. Claim 1 also has been amended to recite that the agent that impedes cell lysis is selected from the group consisting membrane stabilizer, cross-linker, and cell lysis inhibitor. Support for these amendments can be found at least at page 12, paragraph [0064] and at page 25, paragraph [0134].

Claims 9, 14 and 32 have been amended to correct typographical errors.

Claims 10 and 21 have been amended to indicate that the nucleic acid is free nucleic acid. Support for this amendment can be found at least at page 12, paragraph [0064] and at page 25, paragraph [0134].

No new matter is added by the amendments to the claims.

Election/Restriction

Applicant's previous election of Group I, claims 1-23, and 26-33, without traverse is affirmed.

Claims Rejections Under 35 U.S.C. § 102

Claims 1-5, 10-11, 15-17, 21-23 and 26: The Office has rejected claims 1-5, 10-11, 15-17, 21-23 and 26 under 35 U.S.C. 102(b) as being anticipated by Kiessling [US 5,618,664 (1997)]. Applicant respectfully traverses this rejection.

Amended claim 1 recites a method for detecting free nucleic acid comprising: (a) isolating free nucleic acid from a sample, wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor; and (b) detecting the presence or absence of the free nucleic acid. Claims 2-5, 10-11, 15-17, 21-23 and 26 all depend (directly or indirectly) from independent claim 1.

To anticipate a claim, a prior art reference must teach or suggest each and every limitation of the claim. Applicant respectfully submits that Kiessling does not anticipate claims 1-5, 10-11, 15-17, 21-23 and 26 because the reference fails to teach or suggest all elements of claims 1-5, 10-11, 15-17, 21-23 and 26. By contrast to the method of claims 1-5, 10-11, 15-17, 21-23 and 26, which all involve isolating free nucleic acid from a sample, the methods disclosed by Kiessling involve analysis of fixed cells. Kiessling fails to teach or suggest a method comprising isolating free nucleic acid.

Kiessling discloses methods and kits for reducing the transmission of infectious agents contained in biological fluid samples. The methods disclosed in Kiessling involve contacting the biological sample with a fixative solution containing a fixative present at a concentration sufficient to fix analytes contained therein. The methodology disclosed in Kiessling "fixes" leukocytes, and subsequently DNA is isolated from the fixed leukocytes (see col. 10, lines 43-49). Conversely, the

methods of claims 1-5, 10-11, 15-17, 21-23 and 26 are directed toward isolating free nucleic acid. Nowhere does Kiessling teach or suggest a method for detecting free nucleic acid comprising *inter alia* isolating free nucleic acid from a sample.

With regard to the rejection of claim 21, the Examiner stated that "it must be noted (Official Notice) that it was routine in the art at the time of the invention to perform centrifugation step(s) wherein the centrifuge braking power is set to zero. However, the Office has provided absolutely no documentary evidence or rationale in support of its assertion that it was routine in the art to set the centrifuge braking power to zero when purifying free nucleic acid. Applicant asserts that setting the centrifuge braking power to zero is not "capable of instant and unquestionable demonstration as being well known," and therefore must be supported by evidentiary support and/or an adequate technical line of reasoning (MPEP 2144.03). Accordingly, Applicant respectfully requests that proper documentary evidence or an adequate technical line of reasoning required under MPEP 2144.03 be provided in support of the Office's assertion regarding the centrifuge braking power if the rejection is to be maintained.

Since Kiessling does not teach or suggest each and every element of claims 1-5, 10-11, 15-17, 21-23 and 26, Applicant respectfully requests that the rejection of claims 1-5, 10-11, 15-17, 21-23 and 26 under 35 U.S.C. 102(b) be withdrawn.

Claims Rejections Under 35 U.S.C. § 103

Claims 1-9, 26-28 and 33: The Office has rejected claims 1-9, 26-28 and 33 under 35 U.S.C. 103(a) as being unpatentable over Anker *et al.* (Gastroenterology 112: 1114-1120 (1997)) in view of Kiessling (US 5,618,664 (1997)). Applicant respectfully traverses this rejection.

Amended claim 1 recites a method for detecting free nucleic acid comprising: (a) isolating free nucleic acid from a sample, wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor; and (b) detecting the presence or absence of the free nucleic acid. Claims 2-9, 26-28 and 33 all depend (directly or indirectly) from independent claim 1.

The factors a Court considers when determining obviousness and non-obviousness in the United States were outlined by the Supreme Court in Graham et al. v. John Deere Co. of Kansas City et al., 383 U.S. 1 (1966) and are commonly referred to as the "Graham factors." The Court held that obviousness should be determined by looking at: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the difference between the claimed invention and the prior art; and (4) objective evidence of non-obviousness. In addition, the Court outlined several factors that show "objective evidence of non-obviousness" and include commercial success, long-felt need but unsolved needs, and failure of others. In a recent Supreme Court decision, KSR v. Teleflex, the Court re-affirmed the continuing validity of its decision in Graham as the touchstone for an obviousness analysis, stating "there is no necessary inconsistency between the idea underlying the TSM [teaching, suggestion, motivation] test and the Graham analysis" (slip opinion at 15).

Methods for detecting free nucleic acid serve a long felt need in the medical community, including as a method for the detection of cancer. Small amounts of free DNA are found circulating in both healthy and diseased human plasma (Anker *et al.*, page 1114). As discussed in Example 7, paragraph [0626] of the present application, which should not be construed to limit the scope of the invention in any manner, non-invasive methods for the detection of various types of cancer have the potential to reduce morbidity and mortality from the disease. For instance, several techniques for the early detection of colorectal tumors have been developed including colonoscopy, barium enemas, and sigmoidoscopy; however the techniques are limited in use because they are invasive, which causes a low rate of patient compliance.

Methods for detecting free nucleic acid as claimed in claims 1-9, 26-28 may be useful in identifying early stage diseases, including, but not limited to, detecting tumors. However, typically, samples contain only small amounts of free nucleic acid (Anker *et al.*, page 1114), which has limited the clinical utility of free nucleic acid. The methods encompassed within claims 1-9 and 26-28 elevate this problem, and thus provide a solution to a long-felt need in the medical community.

Applicant has discovered that the addition of a cell lysis inhibitor to a sample prior to detecting the presence of free nucleic acid can significantly and unexpectedly increase the proportion of free nucleic acid obtained from the sample. One representative example, which should not be construed to limit the scope of the invention in any manner, demonstrating the impact of using an agent to impede cell lysis is provided in Example 4 of Applicant's specification. In this example, free nucleic acid is fetal nucleic acid but the principal applies to any free nucleic acid. Blood samples were obtained from pregnant women, and each sample was split into two aliquots: one was treated with an agent to impede lysis of cells (formalin) and the other was left untreated. As shown in Example 4, the amounts of fetal DNA isolated from maternal blood samples were significantly, and unexpectedly, higher for samples treated with formalin. As indicated in paragraph [0515] in Example 4, in one set of experiments, the percentage of fetal DNA present in the sample without formalin was 1.56%, whereas the percentage of fetal DNA in the sample treated with formalin was 25%. The high percentage of fetal DNA, which can be obtained from the plasma of maternal blood to which a cell lysis inhibitor (*e.g.* formalin) has been added, is further demonstrated in Example 15 of Applicant's specification (see, *e.g.*, Table XXI and XXII).

Furthermore, the Manual for Patent Examining Procedure states that "greater than expected results are evidence of non-obviousness." *See* MPEP 716.02(a). As discussed above, prior to the Applicants' work, small amounts of free nucleic acid could be obtained from samples. However, using the methods encompassed within claims 1-9 and 26-28 the mean percentage of free nucleic acid obtained from a sample is unexpectedly and significantly increased. Thus, the methods encompassed within claims 1-9 and 26-28 produce unexpected results, and therefore, the claimed methods would not have been obvious to one of ordinary skill in the art.

The Examiner asserts that one of ordinary skill in the art would have been motivated to combine the teachings of Anker *et al.* with the teachings of Kiessling. Applicant respectfully submits that there is no motivation to combine the teachings of the reference Anker *et al.* with the teachings of the reference Kiessling. One of ordinary skill in the art would not be motivated to combine the teachings of Kiessling with Anker *et al.* as the DNA analyzed in the two methods is quite distinct (*i.e*, DNA in Anker *et al.* is free and circulating outside of a cell, while the DNA

analyzed in Kiessling is released from a fixed cell). Anker *et al.* disclose a method that analyzes free tumor DNA. Conversely, the methodology disclosed in Kiessling "fixes" leukocytes, and subsequently DNA is isolated from the fixed leukocytes (see col. 10, lines 43-49). The method disclosed in Anker *et al.* encompasses free DNA while the method disclosed in Kiessling encompass fixing cells and then lysing cells to analyze the analytes therein, which would be of no utility to one of ordinary skill in the art working with free DNA. Thus, there is no motivation to combine the disclosures of Anker *et al.* and Kiessling.

The Examiner states that the ordinary artisan would have been motivated to modify the method of Anker *et al.* using the method of Kiessling in order to protect laboratory personnel performing the assays of Anker *et al.* However, there are numerous methods available to reduce the risk of exposure to infectious agents, and there is no motivation to choose the method disclosed by Kiessling. For example, U.S. Patent No. 5,985,260 discloses a method of disinfecting blood and blood components comprising preparing and immediately adding active albumin-iodine complex to the material to be disinfected. In addition, Moreton and Delves report that the addition of Virkon, which is a viral disinfectant, to clinical samples can reduce the likelihood of infection (Moreton and Delves, J. Anal. At. Spectrom, 1999, 14:893-894). Thus, there are numerous methods available to one of ordinary skill in the art for reducing the risk of exposure to infectious agents, but there is nothing that would lead one of ordinary skill in the art to the specific disclosure of Kiessling.

The methods disclosed in claims 1-9 and 26-28 serve a long-felt need in the medical community, and provide unexpected results, and are therefore non-obvious. In addition, there is no motivation to combine the disclosures of Anker *et al.* and Kiessling, thus, Applicant respectfully requests that the rejection of claims 1-9 and 26-28 under 35 U.S.C. § 103 be withdrawn.

Claims 11-14: The Office has rejected claims 11-14 under 35 U.S.C. 103(a) as being unpatentable over Kiessling (US 5,618,664 (1997)) in view of Leong (5,635,348 (1997)). Applicant respectfully traverses this rejection.

Claims 11-14 depend (directly or indirectly) from independent claim 1, and therefore incorporate all elements of claim 1 as amended. Claims 11-14 are directed further toward the species to which the free nucleic acid belongs.

To establish a *prima facie* case of obviousness, the cited references must teach or suggest each and every claim limitation. The factors a Court considers when determining obviousness and non-obviousness in the United States were outlined by the Supreme Court in Graham et al. v. John Deere Co. of Kansas City et al., 383 U.S. 1 (1966) and are commonly referred to as the "Graham factors." The Court held that obviousness should be determined by looking at: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the difference between the claimed invention and the prior art; and (4) objective evidence of non-obviousness. In addition, the Court outlined several factors that show "objective evidence of non-obviousness" and include commercial success, long-felt need but unsolved needs, and failure of others. In a recent Supreme Court decision, KSR International Co. v. Teleflex, Inc., the Court re-affirmed the continuing validity of its decision in Graham as the touchstone for an obviousness analysis, stating "there is no necessary inconsistency between the idea underlying the TSM [teaching, suggestion, motivation] test and the Graham analysis" (slip opinion at 15).

Moreover, the Patent and Trademark Office published in the Federal Register on October 10, 2007 Examination Guidelines for Determining Obviousness under 35 U.S.C. § 103 in view of the Supreme Court Decision KSR International Co. v. Teleflex, Inc. (72 Federal Register 57526). The Examination Guidelines state that the key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reasons why the claimed invention would have been obvious and identifies seven rationales that can be used to support the legal conclusion of obviousness (see page 57528). One rationale identified in the Federal Register Examination Guidelines at page 57534 is as follows:

> G. Some Teaching, Suggestion or Motivation in the Prior Art That Would Have Led One of Ordinary Skill To Modify the Prior Art Reference or To Combine Prior Art Reference or To Combine Prior Art Reference Teachings To Arrive at the Claimed Invention.

> To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Applicant respectfully submits that the Office has not met its burden of establishing a proper *prima facie* case of obviousness since Kiessling in view of Leong does not teach or suggest a method comprising all of the elements of claims 11-14. Kiessling discloses methods and kits for reducing the transmission of infectious agents contained in biological fluid samples. The methodology disclosed in Kiessling "fixes" leukocytes, and subsequently DNA is isolated from the fixed leukocytes (see col. 10, lines 43-49). Kiessling does not teach or suggest a method comprising *inter alia* isolating free nucleic acid in a sample. Leong discloses methods for identifying bacterial strains in blood. However, Leong does not teach or suggest isolating free nucleic acid. Rather, Leong obtains DNA from lysing bacterial cells. The Leong specification reads:

> DNAs were prepared by ***SDS-proteinase K lysis*** followed by phenol:chloroform extraction. Bacterial strains were obtained from ATCC.

See Leong, col. 14, lines 19-22 (emphasis added). Leong isolates DNA by first lysing the cells using SDS-proteinase K. Conversely, the methods of claims 11-14 are directed toward isolating free nucleic acid in a sample. The combination of Kiessling and Leong does not teach or suggest all elements of claims 11-14 because neither Kiessling nor Leong teach or suggest a method of detecting free nucleic acid comprising *inter alia* isolating free nucleic acid in a sample.

Since Kiessling in view of Leong does not teach or suggest each and every element of claims 11-14, Applicant respectfully requests that the rejection of claims 11-14 under 35 U.S.C. § 103 be withdrawn.

Claims 11 and 18-20: The Office rejected claims 11 and 18-20 under 35 U.S.C. 103(a) as being unpatentable over Kiessling (US 5,618,664 (1997)) in view of Jordan (5,426,026 (1995)). Applicant respectfully traverses this rejection.

Claims 11 and 18-20 depend (directly or indirectly) from independent claim1, and therefore incorporate all elements of claim 1 as amended. Claims 11 and 18-20 are further directed toward the source of the free nucleic acid.

To establish a *prima facie* case of obviousness, the cited references must teach or suggest each and every claim limitation. The factors a Court considers when determining obviousness and non-obviousness in the United States were outlined by the Supreme Court in Graham et al. v. John Deere Co. of Kansas City et al., 383 U.S. 1 (1966) and are commonly referred to as the "Graham factors." The Court held that obviousness should be determined by looking at: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the difference between the claimed invention and the prior art; and (4) objective evidence of non-obviousness. In addition, the Court outlined several factors that show "objective evidence of non-obviousness" and include commercial success, long-felt need but unsolved needs, and failure of others. In a recent Supreme Court decision, KSR International Co. v. Teleflex, Inc., the Court re-affirmed the continuing validity of its decision in Graham as the touchstone for an obviousness analysis, stating "there is no necessary inconsistency between the idea underlying the TSM [teaching, suggestion, motivation] test and the Graham analysis" (slip opinion at 15).

Moreover, the Patent and Trademark Office published in the Federal Register on October 10, 2007 Examination Guidelines for Determining Obviousness under 35 U.S.C. § 103 in view of the Supreme Court Decision KSR International Co. v. Teleflex, Inc. (72 Federal Register 57526). The Examination Guidelines state that the key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reasons why the claimed invention would have been obvious and identifies seven rationales that can be used to support the legal conclusion of obviousness (see page 57528). One rationale identified in the Federal Register Examination Guidelines at page 57534 is as follows:

H. Some Teaching, Suggestion or Motivation in the Prior Art That Would Have Led One of Ordinary Skill To Modify the Prior Art Reference or To Combine Prior Art Reference or To Combine Prior Art Reference Teachings To Arrive at the Claimed Invention.

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Applicant respectfully submits that the Office has not met its burden of establishing a proper *prima facie* case of obviousness since Kiessling in view of Jordan does not teach or suggest a method comprising all of the elements of claims 11 and 18-20. Kiessling discloses methods and kits for reducing the transmission of infectious agents contained in biological fluid samples. The methodology disclosed in Kiessling "fixes" leukocytes, and subsequently DNA is isolated from the fixed leukocytes (see col. 10, lines 43-49). Kiessling does not teach or suggest a method comprising *inter alia* isolating free nucleic acid in a sample. Jordan discloses a method for diagnosing a species of Candida in a patient, wherein cells are lysed and the DNA is analyzed. The Jordan specification reads as follows:

> The method includes the steps of: i) collecting a blood sample from the patient; ii) separating out the plasma and the buff coat layer fractions present in the blood sample; iii) enzymatically digesting non-yeast DNA present in the remaining fractions; iv) ***enzymatically digesting the cell wall of yeast present in the remaining fractions in order to release DNA present in the cells***....

Col. 3, lines 18-25 (emphasis added). Jordan discloses a method that analyzes DNA contained with the cell. Conversely, the methods of claims 11 and 18-20 are directed toward isolating free nucleic acid in a sample. The combination of Kiessling and Jordan does not teach or suggest all elements of claims 11 and 18-20 because neither Kiessling nor Jordan teach or suggest a method of detecting free nucleic acid comprising *inter alia* isolating free nucleic acid in a sample.

Since Kiessling in view of Jordan does not teach or suggest each and every element of claims 11 and 18-20, Applicant respectfully requests that the rejection of claims 11 and 18-20 under 35 U.S.C. § 103 be withdrawn.

Claims 1 and 29-32: The Office has rejected claims 1 and 29-32 under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.* (US 5,576,176 (1996)) in view of Kiessling (US 5,618,664 (1997)). Applicant respectfully traverses this rejection.

As stated above, amended claim 1 recites a method for detecting free nucleic acid comprising: (a) isolating free nucleic acid from a sample, wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor; and (b) detecting the presence or absence of the free nucleic acid. Claims 29-32 depend (directly or indirectly) from independent claim 1, and therefore incorporate all elements of claim 1 as amended.

To establish a *prima facie* case of obviousness, the cited references must teach or suggest each and every claim limitation. The factors a Court considers when determining obviousness and non-obviousness in the United States were outlined by the Supreme Court in Graham et al. v. John Deere Co. of Kansas City et al., 383 U.S. 1 (1966) and are commonly referred to as the "Graham factors." The Court held that obviousness should be determined by looking at: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the difference between the claimed invention and the prior art; and (4) objective evidence of non-obviousness. In addition, the Court outlined several factors that show "objective evidence of non-obviousness" and include commercial success, long-felt need but unsolved needs, and failure of others. In a recent Supreme Court decision, KSR International Co. v. Teleflex, Inc., the Court re-affirmed the continuing validity of its decision in Graham as the touchstone for an obviousness analysis, stating "there is no necessary inconsistency between the idea underlying the TSM [teaching, suggestion, motivation] test and the Graham analysis" (slip opinion at 15).

Moreover, the Patent and Trademark Office published in the Federal Register on October 10, 2007 Examination Guidelines for Determining Obviousness under 35 U.S.C. § 103 in view of the Supreme Court Decision KSR International Co. v. Teleflex, Inc. (72 Federal Register 57526). The Examination Guidelines state that the key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reasons why the claimed invention would have been obvious and identifies seven rationales that can be used to support the legal conclusion of obviousness (see page 57528). One rationale identified in the Federal Register Examination Guidelines at page 57534 is as follows:

> I. Some Teaching, Suggestion or Motivation in the Prior Art That Would Have Led One of Ordinary Skill To Modify the Prior Art Reference or To Combine Prior Art Reference or To Combine Prior Art Reference Teachings To Arrive at the Claimed Invention.
>
> To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Applicant respectfully submits that the Office has not met its burden of establishing a proper *prima facie* case of obviousness since Adams *et al.*, either alone or in combination, with Kiessling does not teach or suggest a method comprising all of the elements of claims 1 and 29-32. Adams *et al.* disclose a method for detection and monitoring of HIV latency and activation by analyzing RNA isolated from cells. The Adams specification reads as follows:

> RNA was isolated from $2x10^6$ cultured cells or freshly isolated PBMC (Peripheral Blood Mononuclear Cell)...

See col. 19, lines 19-20.

> RNA was isolated from U1 cells ***by the lysis of cells with guanidinium isothiocyanate*** followed by centrifugation through a cesium chloride solution as previously described.

See col. 21, lines 32-35. The methodology disclosed by Adams *et al.* lyses cells to release RNA, which is subsequently analyzed. Conversely, the methods of claims 1 and 29-32 are directed toward isolating free nucleic acid in a sample. Kiessling discloses methods and kits for reducing the transmission of infectious agents contained in biological fluid samples. The methodology disclosed in Kiessling "fixes" leukocytes, and subsequently DNA is isolated from the fixed leukocytes (*see* col. 10, lines 43-49). Kiessling does not teach or suggest a method for detecting free nucleic acid comprising *inter alia* isolating free nucleic acid. The combination of Adams *et al.* and Kiessling does not teach or suggest all elements of claims 1 and 29-32 because neither Adams *et al.* nor Kiessling teach or suggest a method of detecting free nucleic acid comprising *inter alia* isolating free nucleic acid in a sample.

Since Adams *et al.* in view of Kiessling does not teach or suggest each and every element of claims 1 and 29-32, Applicant respectfully requests that the rejection of claims 1 and 29-32 under 35 U.S.C. § 103 be withdrawn.

Non-Statutory Obviousness-type Double Patenting Rejection

Claims 1-6 and 33: Claims 1-6 and 33 are rejected provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 87-91 of copending Application No. 10/661,165 in view of Anker *et al.* (Gastroenterology 112: 1114-1120 (1997)). By virtue of this amendment, claim 33 has been cancelled, and thus the rejection of claim 33 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 87-91 of copending Application No. 10/661,165 in view of Anker *et al.* (Gastroenterology 112: 1114-1120 (1997)) is moot.

Applicant notes that this is a provisional rejection only. Applicant will address this rejection, if maintained, at the appropriate time if conflicting claims are found allowable.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 543312000401. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 17, 2007

Respectfully submitted,

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